METABOLOMIC AND GENOMIC MARKERS OF ATHEROSCLEROSIS AS RELATED TO OXIDATIVE STRESS, INFLAMMATION, AND VASCULAR FUNCTION IN TWIN ASTRONAUTS

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BACKGROUND

Future human space travel will consist primarily of long-duration missions onboard the International Space Station (ISS) or exploration-class missions to Mars, its moons, or nearby asteroids. Astronauts participating in long-duration missions may be at an increased risk of oxidative stress and inflammatory damage due to radiation, psychological stress, altered physical activity, nutritional insufficiency, and hyperoxia during extravehicular activity. By studying one identical twin during his 1-year ISS mission and one ground-based twin, this work extends a current NASA-funded investigation to determine whether these spaceflight factors contribute to an accelerated progression of atherosclerosis. This study of twins affords a unique opportunity to examine the spaceflight-related atherosclerosis risk independent of the confounding factors associated with different genotypes.

PURPOSE

The purpose of this investigation is to determine whether biomarkers of oxidative and inflammatory stress are elevated during and after long-duration spaceflight and determine if a relation exists between levels of these biomarkers and structural and functional indices of atherosclerotic risk measured in the carotid and brachial arteries. These physiological and biochemical data will be extended by using an exploratory approach to investigate the relationship between intermediate phenotypes and risk factors for atherosclerosis and the metabolomic signature from plasma and urine samples. Since metabolites are often the indirect products of gene expression, we will simultaneously assess gene expression and DNA methylation in leukocytes.

HYPOTHESIS

We predict that the space-flown twin will experience elevated biomarkers of oxidative stress and inflammatory damage, altered arterial structure and function, accelerated telomere shortening, dysregulation of genes associated with oxidative stress and inflammation, and a metabolic profile shift that is associated with elevated atherosclerosis risk factors. Conversely, these will not be observed in the ground-based twin.

METHODS

We will measure blood and urine biomarkers of oxidative stress and inflammation as well as arterial structure and function (carotid intima-medial thickness and brachial artery flow-mediated dilation) in one twin astronaut before, during, and after long-duration spaceflight and in his twin serving as a ground-based control. Furthermore, we will measure metabolomics (targeted and untargeted approaches) and genomic markers (DNA methylation, mRNA gene expression, telomere length) to elucidate the molecular mechanisms involved. A panel of biomarkers of oxidative and inflammatory stress will be measured in venous blood samples and 24-h (in-flight) and 48-h (pre- and post-flight) urine pools twice before flight, early (flight days 15 and 60) and late (2 weeks before landing) during the mission, and early in the post-flight recovery phase (~3-5 days after landing). Arterial structure, assessed from measures of intima-media thickness, will be measured at the same times. Arterial function will be assessed using brachial flow-mediated dilation, a well-validated measure used to assess endothelium-dependent vasodilation and a sensitive predictor of atherosclerotic risk, only before and after spaceflight.

DISCUSSION

Pre- and in-flight data collection is in progress for the space-flown twin, and similar data have been obtained from the ground-based twin. Blood and urine samples will be batch processed when received from ISS after the conclusion of the 1-year mission. Results from these individual subjects will be compared to the larger complement of subjects participating in the companion study currently ongoing in ISS astronauts.

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